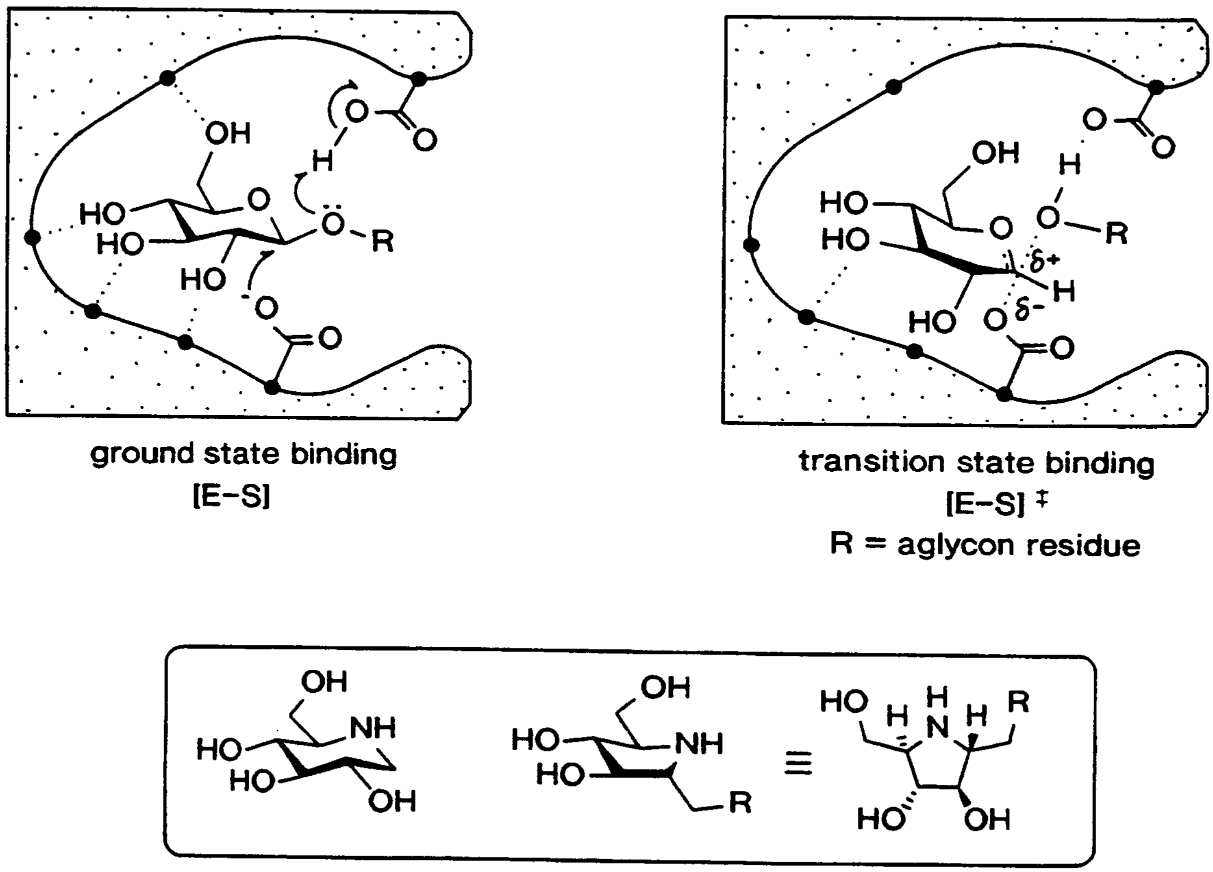
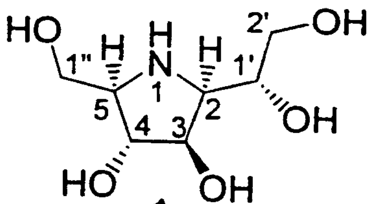
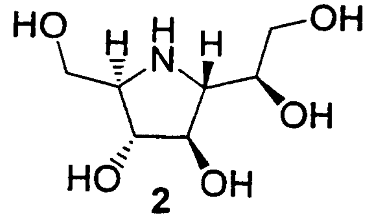

ground state binding
[E−S]
transition state binding
[E−S] ‡
R = aglycon residue

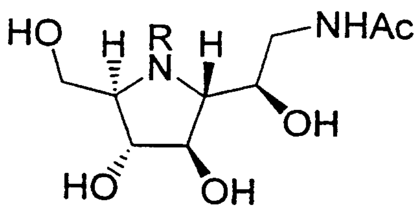
FIG. 1



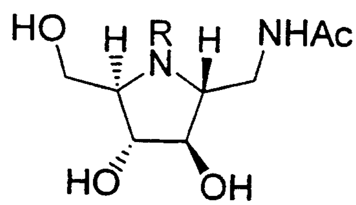
1



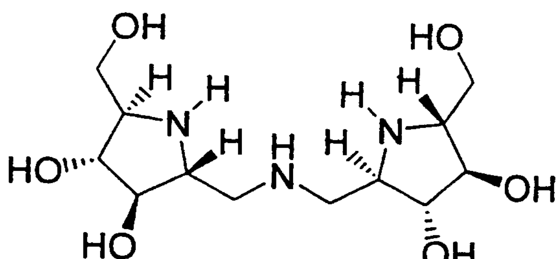
2



6 R = H
7 R = CH_3
8 R = CH_2CH_3



3 R = H
4 R = CH_3
5 R = $(CH_2)_3CH_3$



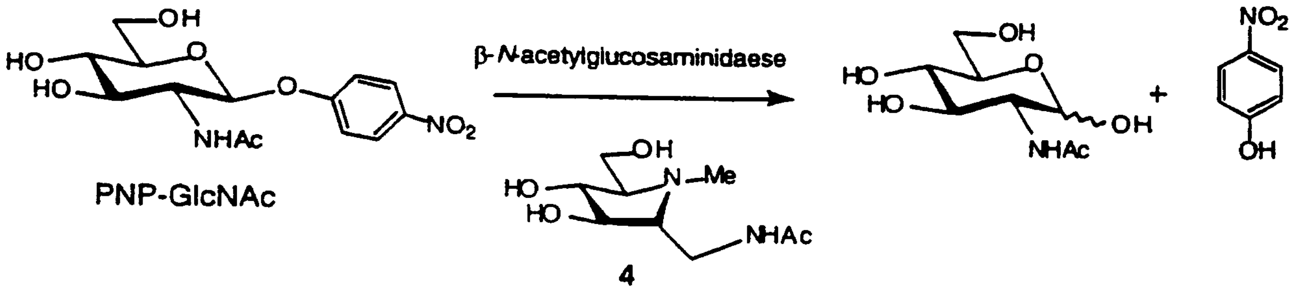
9

FIG. 2

compd	α-glucosidase[a] *Saccaromyces sp*	β-glucosidase[b] sweet almond	β-*N*-acetylglucosaminidase bovine kidney[c]	β-*N*-acetylhexosaminidase human placenta A[d]	β-*N*-acetylhexosaminidase p[e]
	K_i (μM)				
1[f]	330	50	-[h]	-	-
2[f]	28	2.6	-	-	-
3	380	*[g]	2.9×10^{-1}	2.2×10^{-1}	2.6×10^{-1}
4	ni	ni	1.1×10^{-1}	1.4×10^{-1}	8.0×10^{-2}
5	ni	ni	1.3	5.1×10^{-1}	2.4×10^{-1}
6	*	2.2	*	-	-
7	*	45	*	-	-
8	ni	120	ni[i]	-	-
9	53	37	-	-	-

[a] K_m = 0.30 mM, V_{max} = 0.7 (μM/s)/mg. [b] K_m = 3.2 mM, V_{max} = 3.2 (μM/s)/mg. [c] K_m = 4.1 mM, V_{max} = 6.4 (μM/s)/mg. [d] K_m = 2.5 mM, V_{max} = 2.1 (μM/s)/mg. [e] K_m = 2.8 mM, V_{max} = 2.3 (μM/s)/mg. [f] Preliminary assay result using photometric assay gave K_i values: 430 and 18 μM for compound **1** and 7.2 and 7.6 μM for compound **2** toward α-glucosidase and β-glucosidase, respectively. See also refs 6a and 19. [g] *: poor inhibitor with IC_{50} above 0.5 mM. [h] -: not tested. [i] ni: not inhibitor.

FIG. 3


PNP-GlcNAc
β-N-acetylglucosaminidaese
4
NHAc
N—Me
OH
HO
NO_2

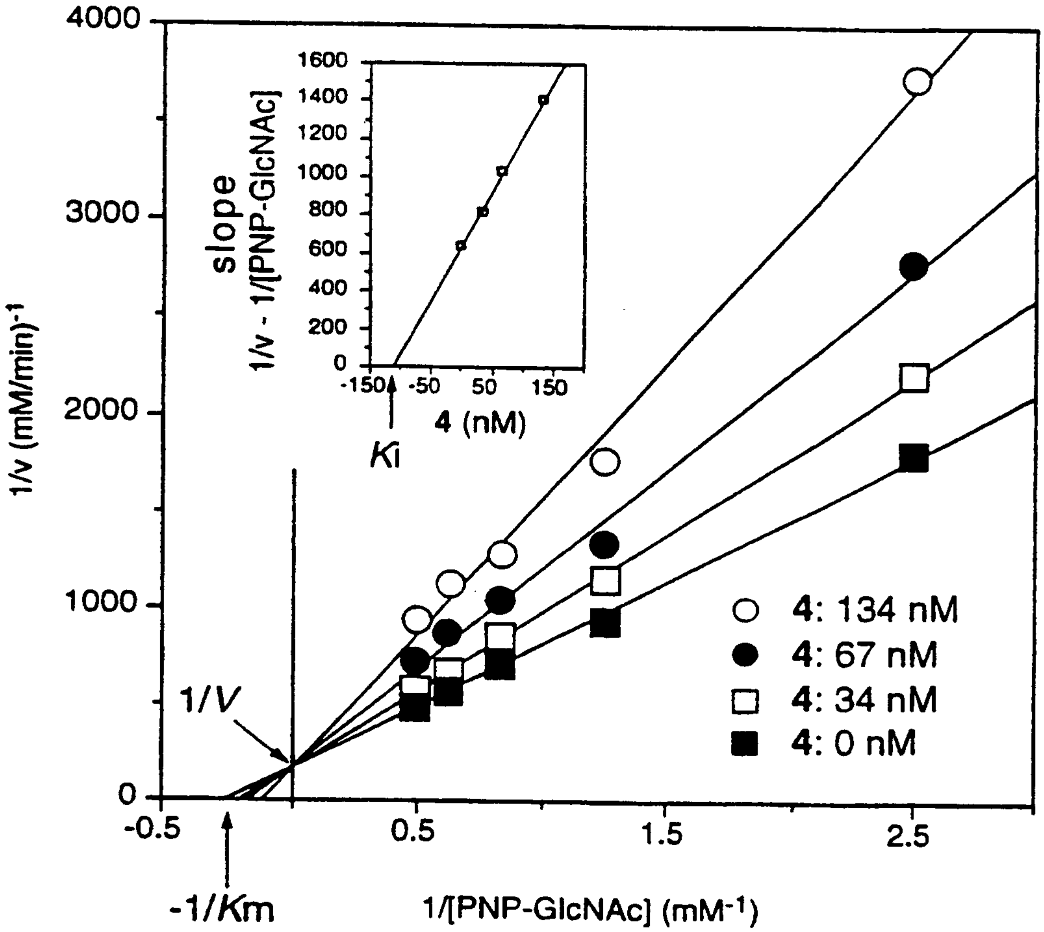
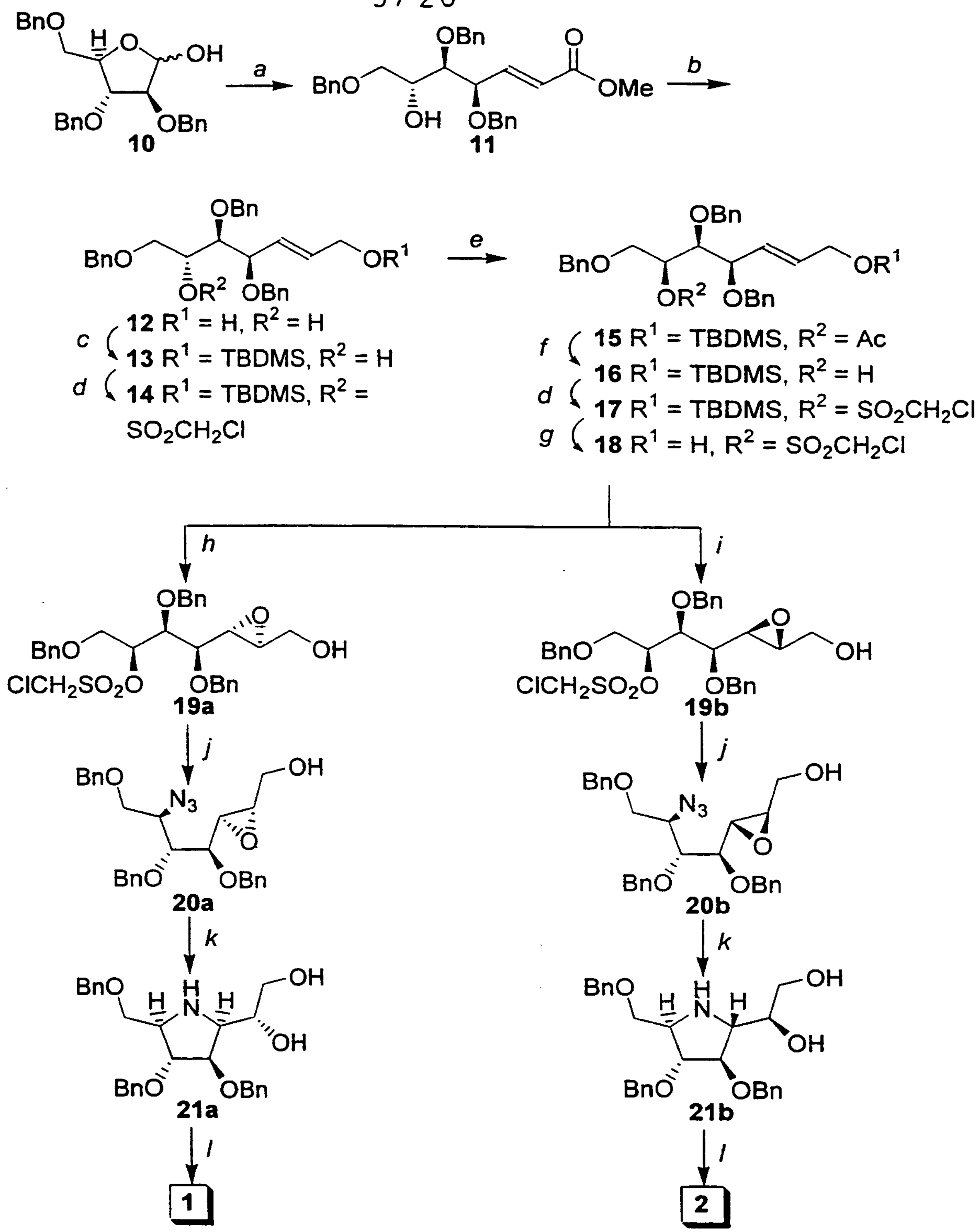
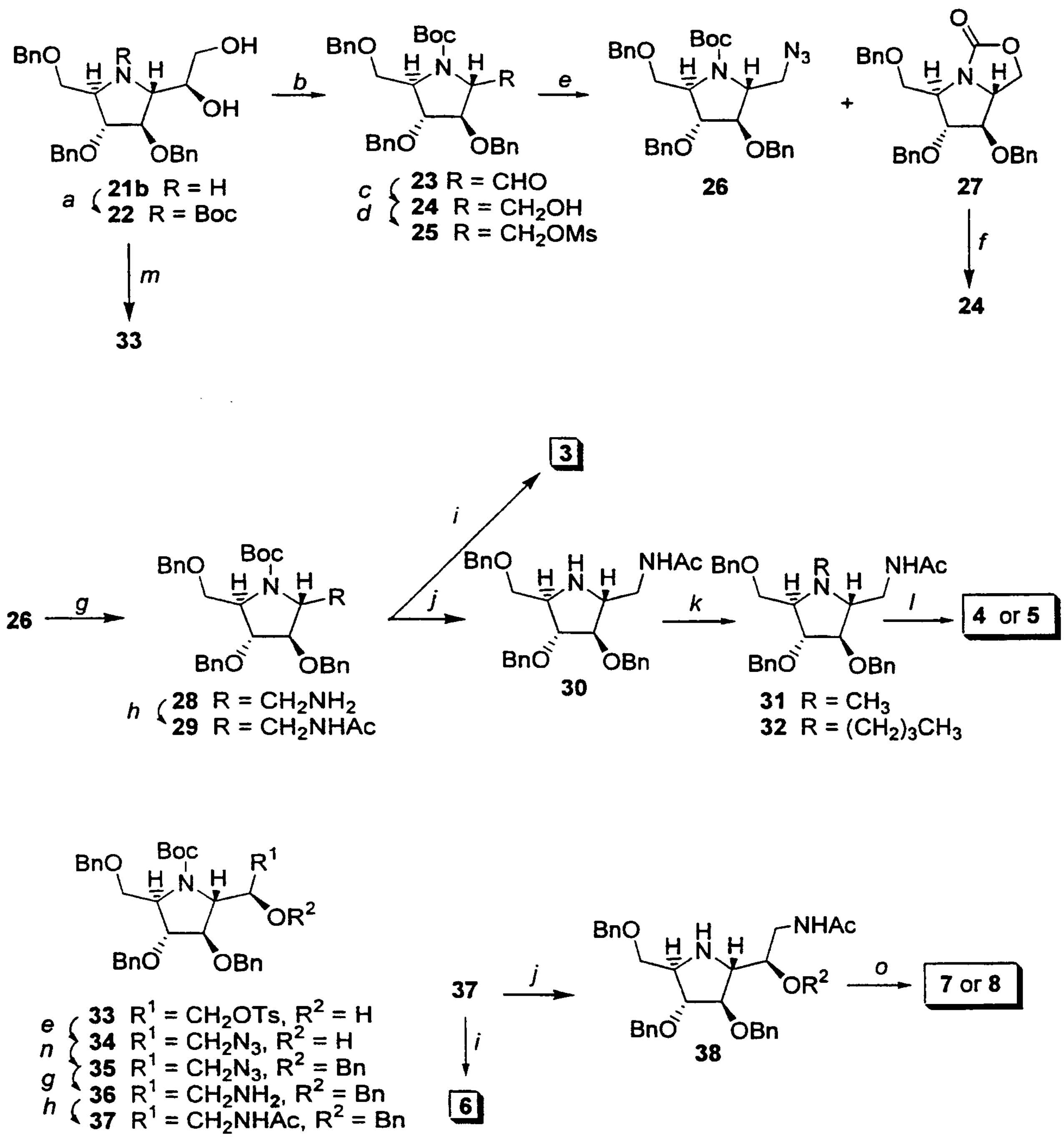

1/v (mM/min)-1
1/[PNP-GlcNAc] (mM-1)
-1/Km
1/V
4: 134 nM
4: 67 nM
4: 34 nM
4: 0 nM
slope
1/v - 1/[PNP-GlcNAc]
4 (nM)
Ki

FIG. 4



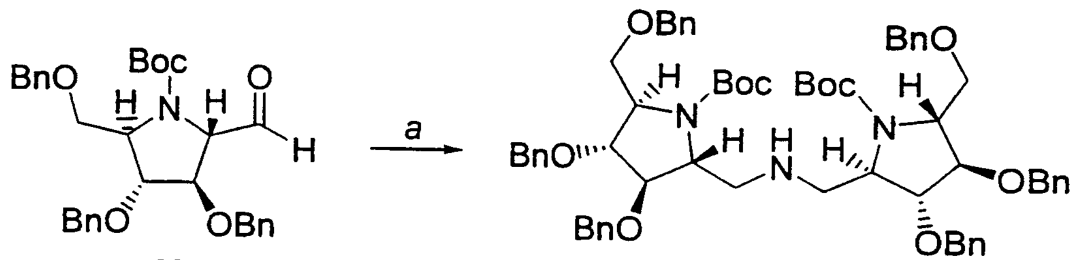
a $Ph_3P^+{=}CHCO_2Me{\cdot}\ {}^-OAc$ / benzene; *b* DIBAL / CH_2Cl_2; *c* TBDMSCl - Et_3N -DMAP / DMF; *d* $ClCH_2SO_2Cl$ - Pyr.; *e* CsOAc - 18-crown-6 / toluene; *f* NaOMe; *g* 1N-HCl / THF; *h* *t*-BuOOH - Ti(O-*i*-Pr)$_4$ - L-(+)-diethyltartrate - MS 4A / CH_2Cl_2; *i* *t*-BuOOH - Ti(O-*i*-Pr)$_4$ - D-(-)-diethyltartrate - MS 4A / CH_2Cl_2; *j* NaN_3 / DMF; *k* Ph_3P / THF; *l* H_2 - Pd/C / MeOH.

FIG. 5



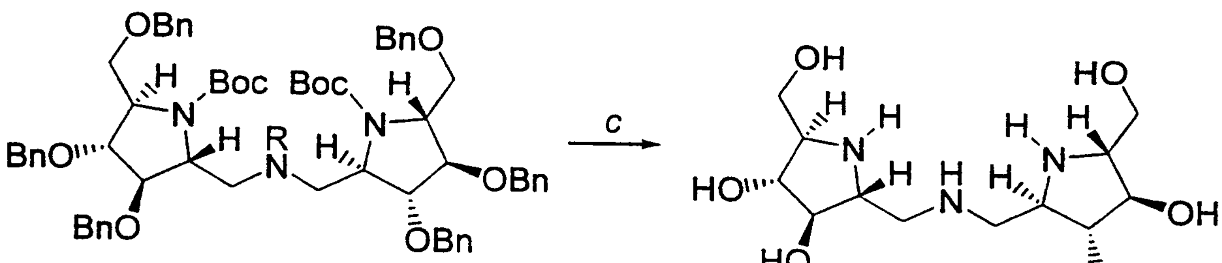
a $(Boc)_2O$ - Et_3N / CH_2Cl_2; *b* $Pb(OAc)_4$ / toluene; *c* DIBAL / CH_2Cl_2; *d* MsCl - Et_3N / CH_2Cl_2; *e* NaN_3 / DMF; *f* 1) $LiAlH_4$ / THF, 2) $(Boc)_2O$ - Et_3N / CH_2Cl_2; *g* H_2 - Pd/C / MeOH; *h* Ac_2O - Pyr.; *i* 1) H_2 - Pd/C / MeOH - HCl, 2) TFA; *j* TFA; *k* CH_2O or $CH_3(CH_2)_2CHO$ - $NaBH_3CN$ / MeOH; *l* H_2 - Pd/C / MeOH - HCl; *m* TsCl - Pyr.; *n* BnBr - Ag_2O - KI / DMF; *o* 1) CH_2O or CH_3CHO - $NaBH_3CN$ / MeOH, 2) H_2 - Pd/C / MeOH - HCl.

FIG. 6



23

39



b 39 R = H
40 R = Boc

9

a NH_4OAc - $NaBH_3CN$ / MeOH; *b* $(Boc)_2O$ - Et_3N / CH_2Cl_2; *c* 1) Pd/C / MeOH - HCl, 2) TFA.

FIG. 7

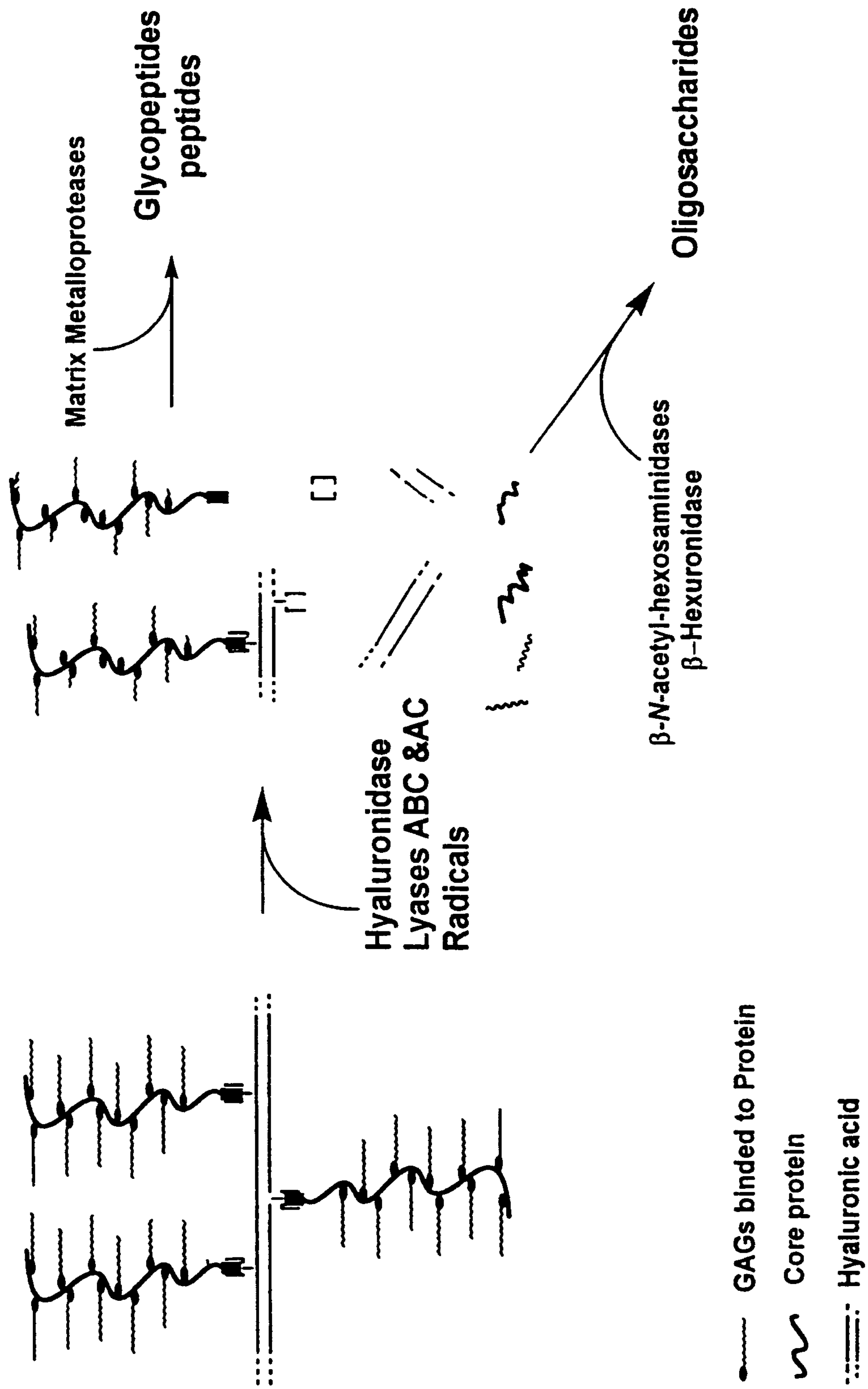

Matrix Metalloproteases
Glycopeptides
peptides
Oligosaccharides
Hyaluronidase
Lyases ABC &AC
Radicals
β-N-acetyl-hexosaminidases
β-Hexuronidase
GAGs binded to Protein
Core protein
Hyaluronic acid

FIG. 8

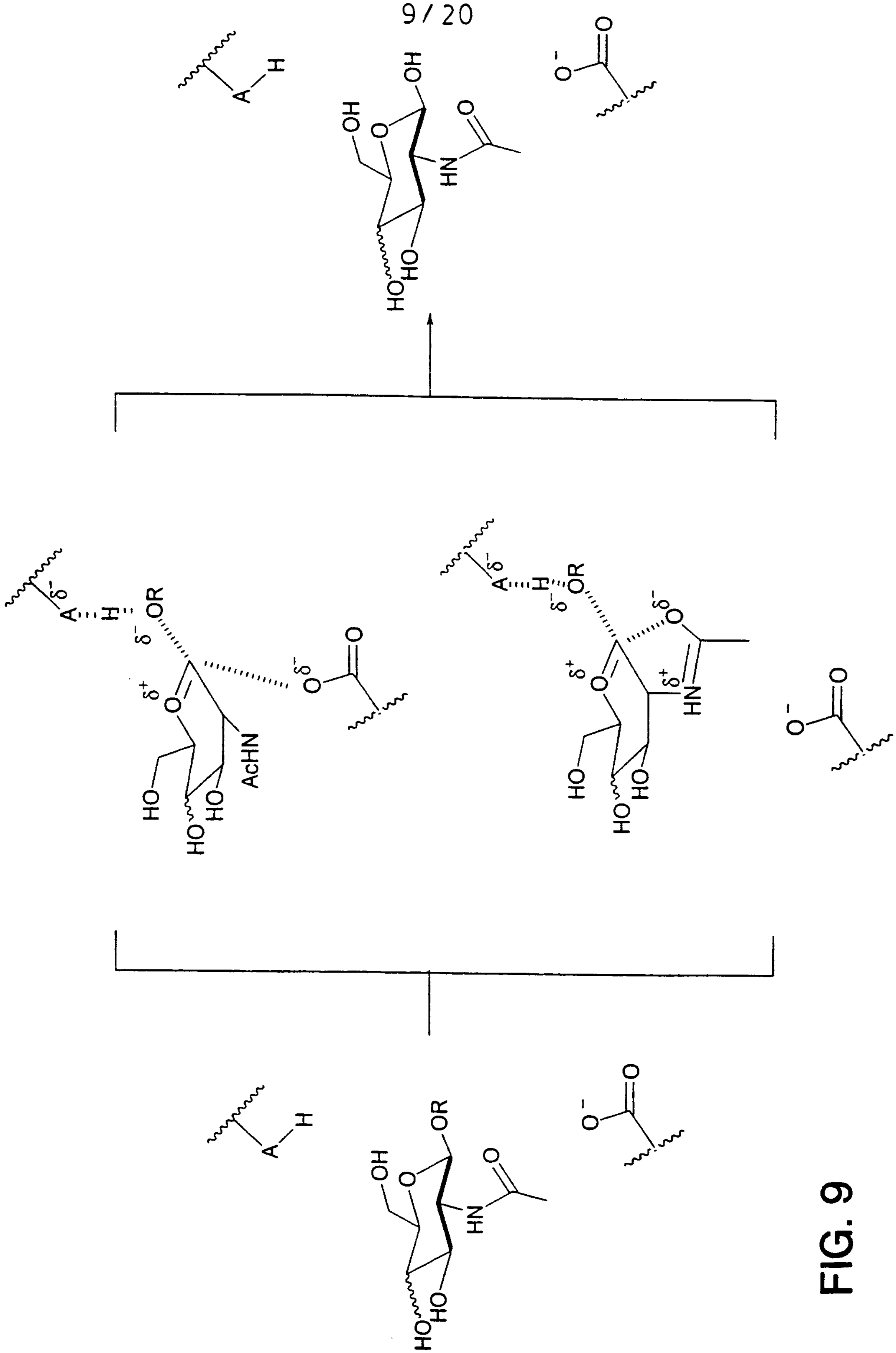
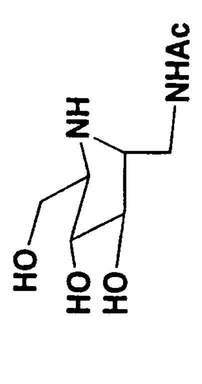
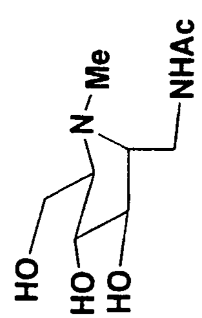


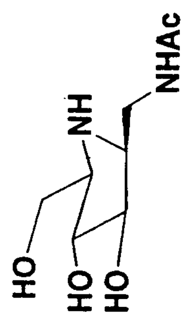
FIG. 9



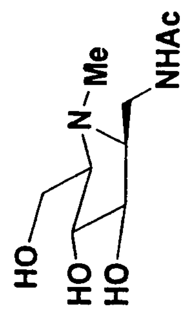
3



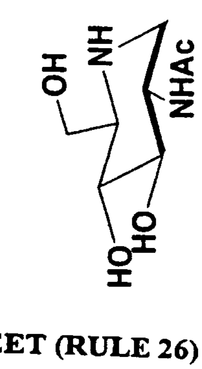
4



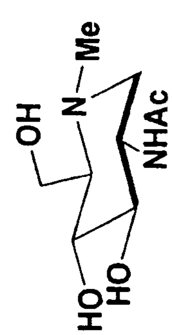
103



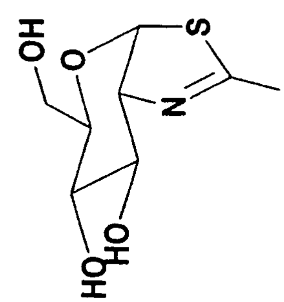
104



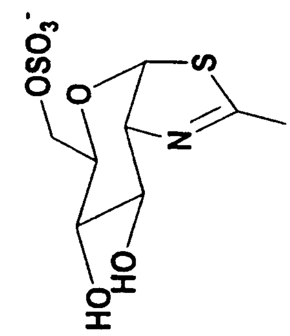
105



106

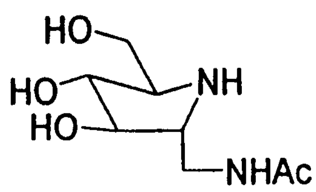
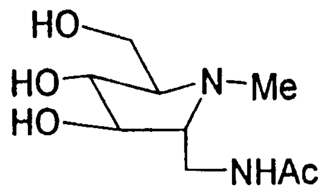
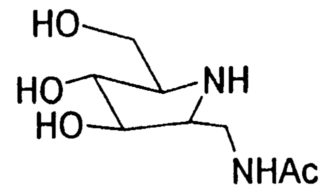
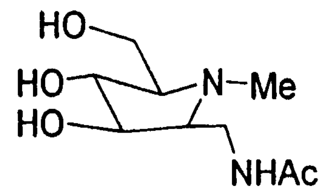


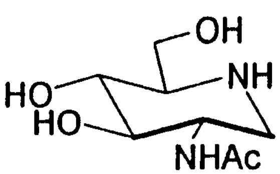
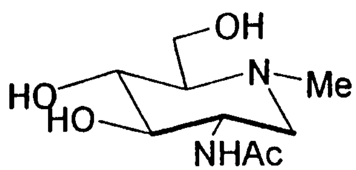
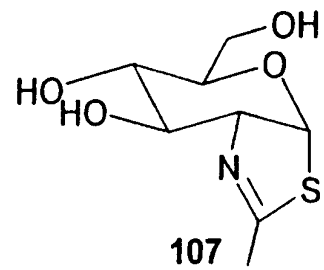
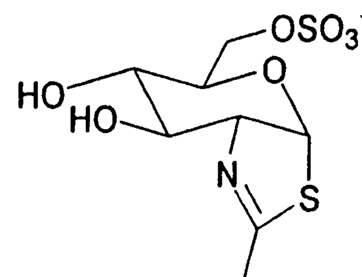
107



108

FIG. 10

	 3	 4	 103	 104
Ki	—	24nM	—	—

	 105	 106	 107	 108
Ki	1200nM	860nM	IC_{50}MUG<IC_{50}MUGS ~ 10µm	IC_{50}MUG=100µm IC_{50}MUGS<10µm

— Not assayed yet

FIG. 11

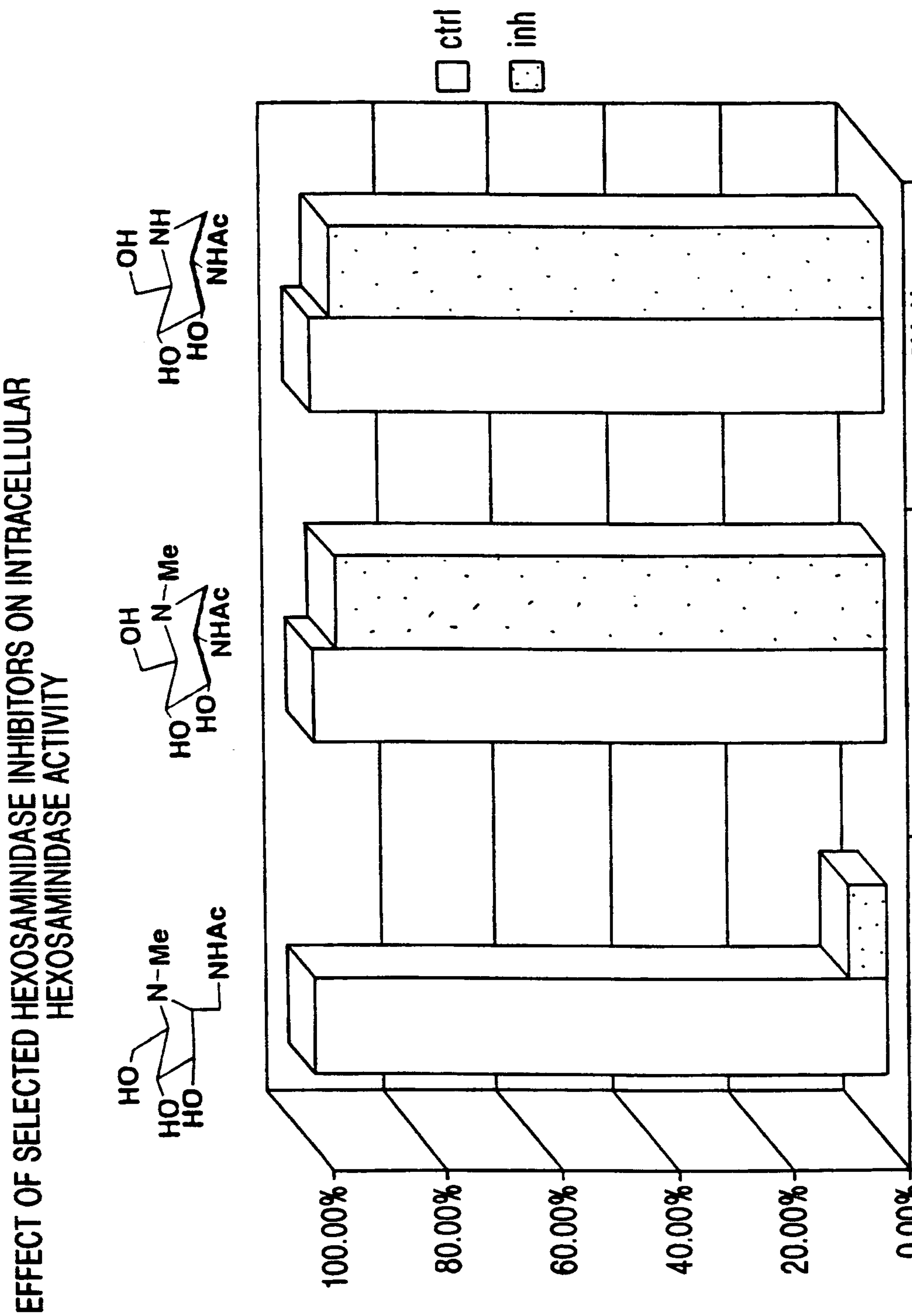

EFFECT OF SELECTED HEXOSAMINIDASE INHIBITORS ON INTRACELLULAR HEXOSAMINIDASE ACTIVITY
ctrl
inh
100.00%
80.00%
60.00%
40.00%
20.00%
0.00%
5M-N-CH3
6M-N-CH3
6M-N
HO
HO
HO
N-Me
NHAc
OH
NH

FIG. 12

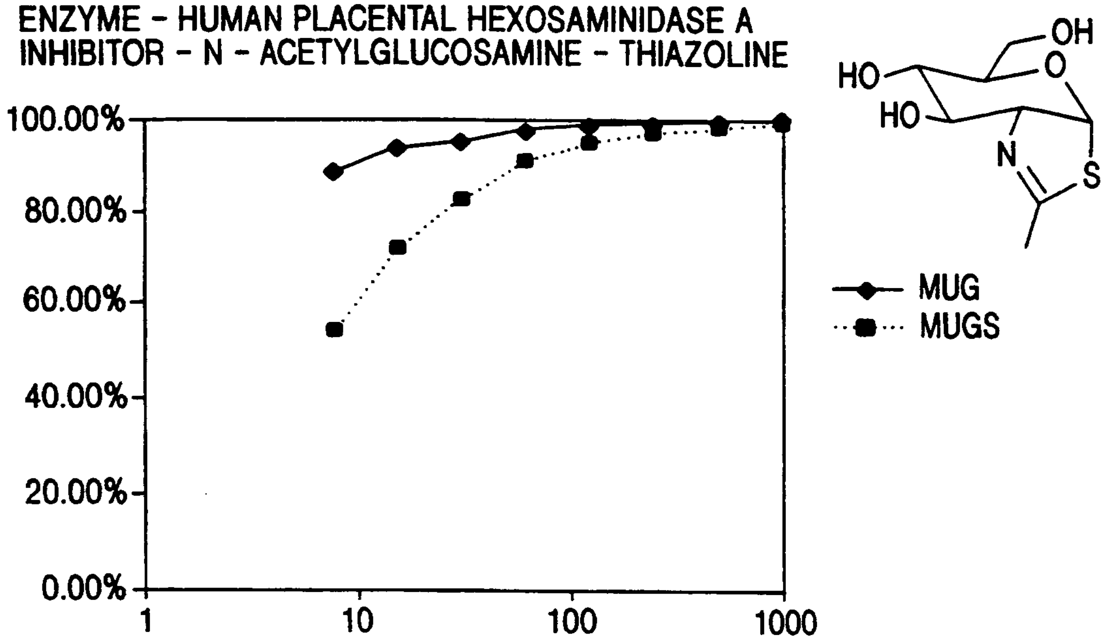


FIG. 13A

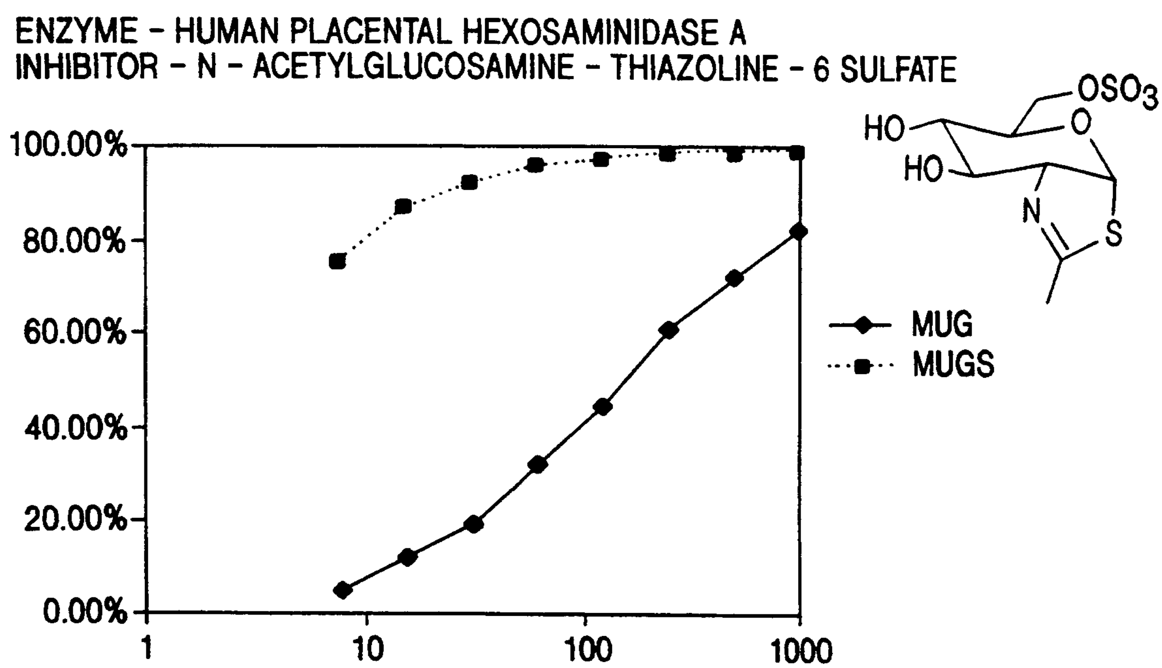
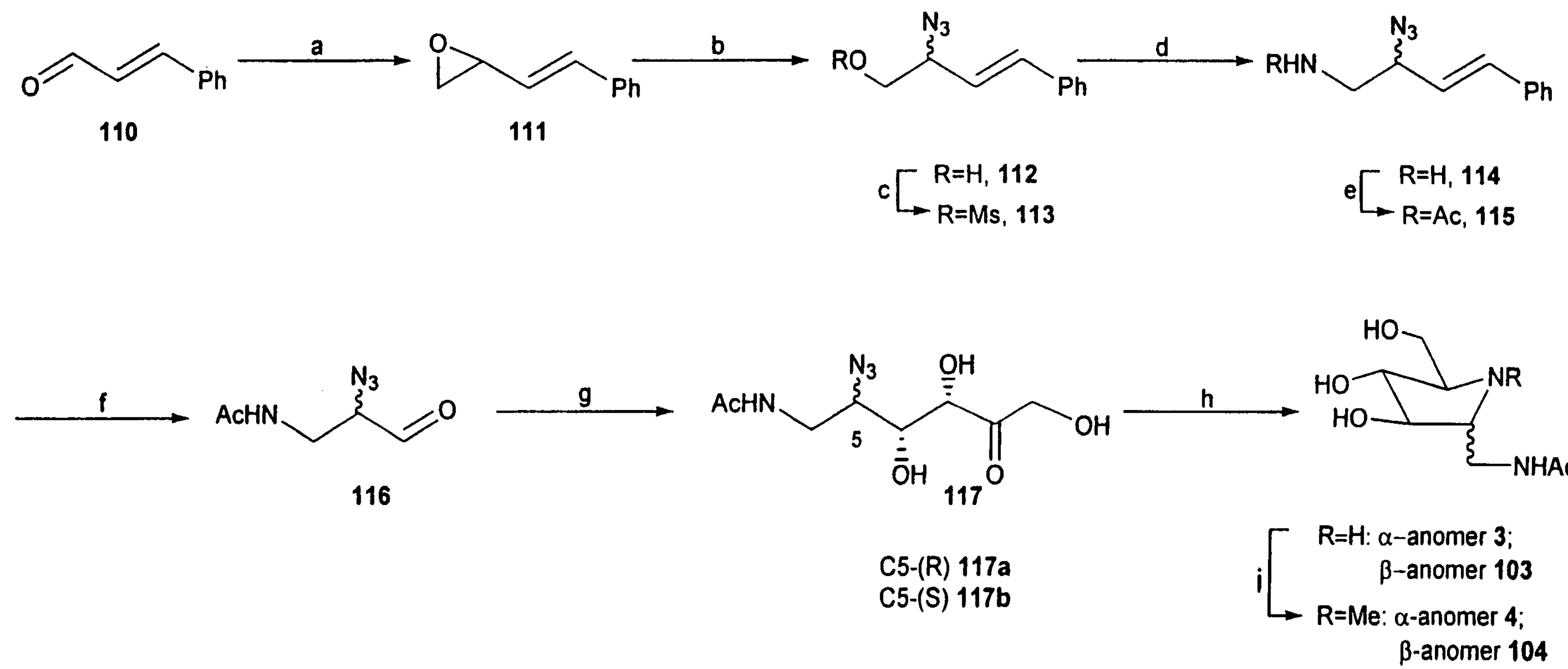
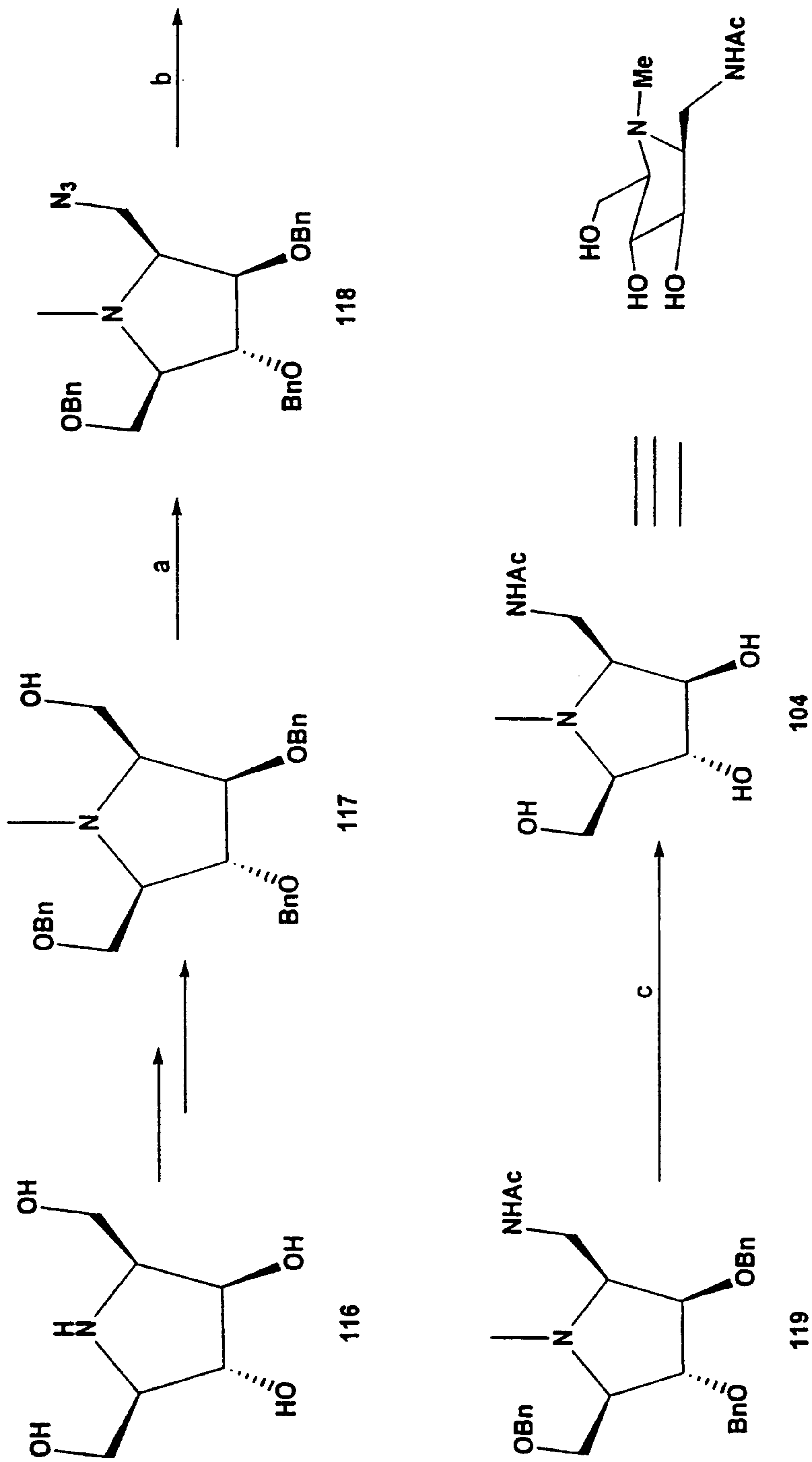


FIG. 13B



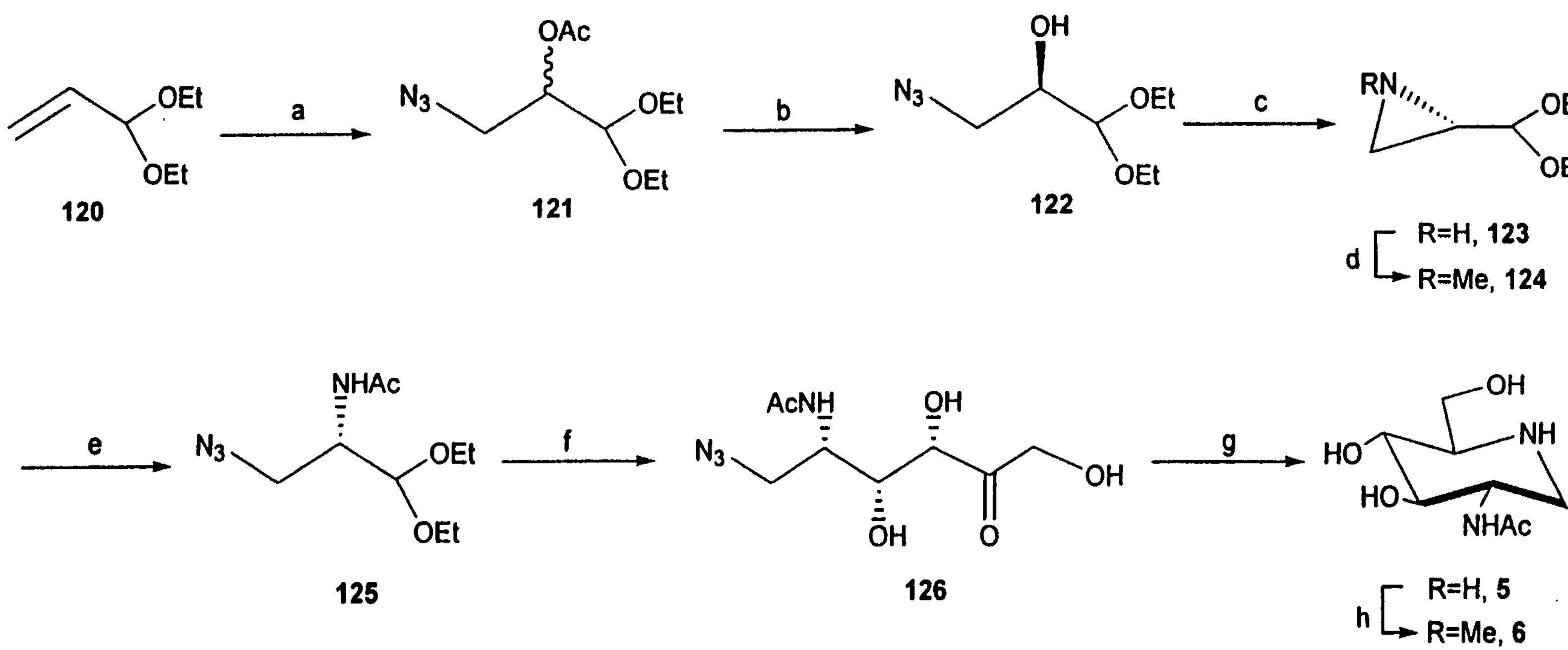
a. Me_3S^+I/NaH, DMSO/THF; b. NaN_3, acetone/H_2O, 82% from **110**: c. MsCl, Pyr. 96%; d. HMTA, NaI/EtOH; HCl, 65°C; e. isopropenyl acetate, 85% from **113**; f. O_3, Me_2S; g. DHAP, RAMA, pH=6.5; acid pase 37°C, pH=4.7; 44% for (R), 30% for (S); h. Pd-C/H_2, 80%; i. CH_2O, Pd-C/H_2, 90%.

FIG. 14



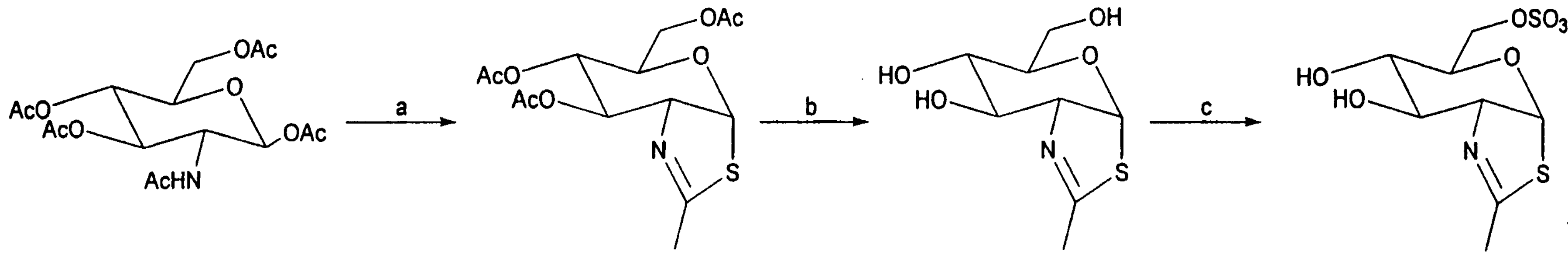
a. MsCl, Pyr; NaN$_3$, CH$_2$Cl$_2$, 87% for 2 steps; b. PPh$_3$, THF; Ac$_2$O, Pyr. 87% from 118; c. Pd-C/H$_2$ 50 psi, 89%.

FIG. 15



a. H_2O_2, PhCN; NaN_3, pH=7.5; Ac_2O, Pyr. 76% for 3 steps; b. PS-80, pH=7.0, 45%, 98%ee; c. Ph_3P, toluene, 120°C; d. Ac_2O, K_2CO_3, 30% for 2 steps; e. NaN_3, $ZnCl_2/Et_2O$, DMF 75°C, 62%; f. pH=1, 45°C; DHAP, RAMA, pH=6.5; pH=4.7, acid pase, 37°C, 55% for 3 steps; g. Pd-C/H_2, 87%; CH_2O, Pd-C/H_2, 92%.

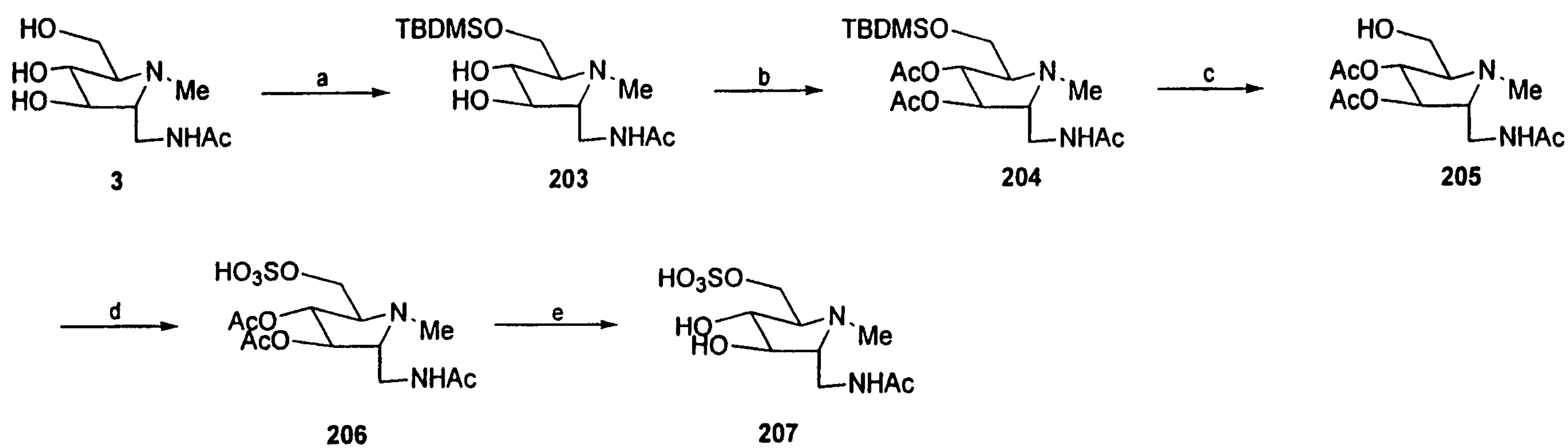
FIG. 16



127 128 107 108

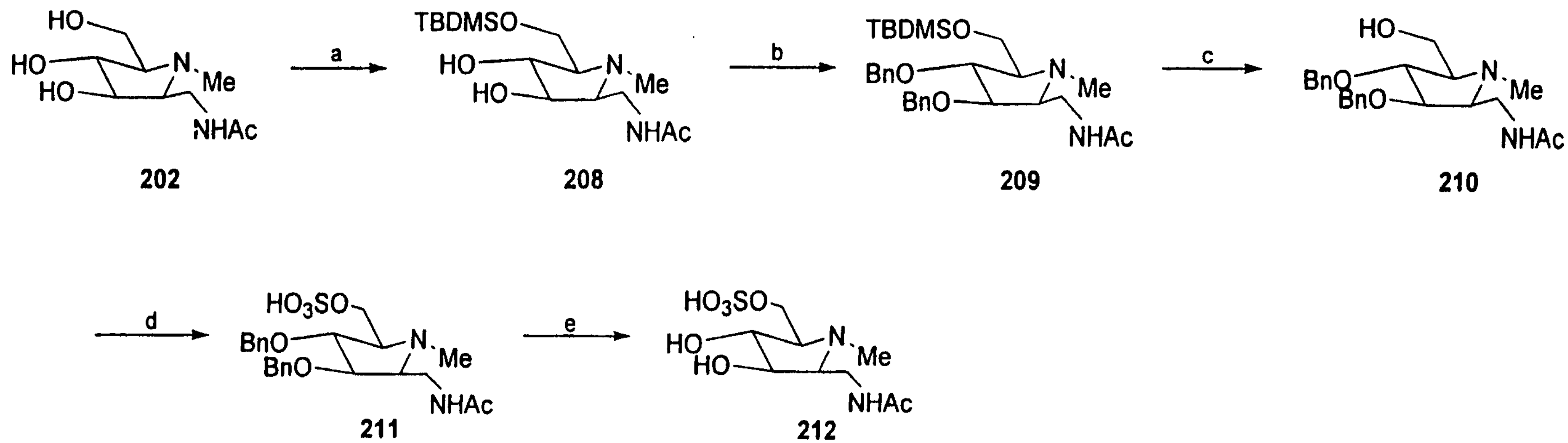
a. Lawesson's reagent, toluene, 80°C; b. MeONa/MeOH, 85% for 2 steps; c. $SO_3 \cdot NMe_3$, Pyr. 0°C, 87%.

FIG. 17



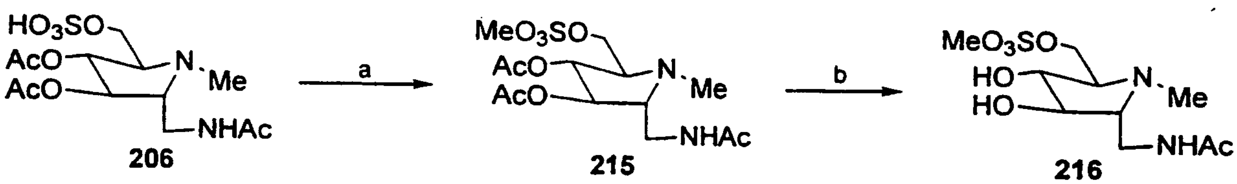
a. TBDMSCl, TEA, 0°C, DMF, overnight, 88%; b. Ac_2O, Pyridine, 0°C-rt. ; c. $AcOH/H_2O/THF$(5:1:3), 50°C. overnight, 75% for two steps; d. SO_3/Pyr, pyridine, 25 °C. 82%; e. cat. MeONa, MeOH, 85%

FIG. 18



a. TBDMSOTf, TEA, 0 °C, DMF, 1.0 h, 90%; b. BnBr, NaH, 0 °C - 25 °C, 90%; c. TBAF, THF, 0 °C - 25 °C, 4h, 80%; d. SO_3/Pyr, pyridine, 25 °C, 80%; e. $Pd(OH)_2$/C, H_2, 75%

FIG. 19



a. MeOH, 50°C, 1h, 90%; b. MeONa (cat.), MeOH, 3h, 80%.

FIG. 20